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Bezeichnung: Self-forming phospholipid gels

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Die angehefteten Stücke sind eine richtige und genaue Wiedergabe der ursprünglichen Unterlagen dieser Patentanmeldung.

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Self-forming Phospholipid Gels

The invention discloses self-forming gels consisting of natural, semi-synthetic or synthetic phospholipids and water.

The gels may be used as such as moisturizing or mollifying treatment of skin, mucosal skin, natural or surgical body cavities, or contain a pharmacologically active agent that is released onto or into the skin, mucosa, natural or surgical body cavity or compartment.

Phospholipids in the form of liposomes have been employed as topical drug carriers *[Schreier & Bouwstra, J. Control. Release 30, 1-15, 1994; Cevc, Crit. Rev. Ther. Drug Carrier Syst. 13, 257-288, 1996; Yarosh, Photodermatol. Photoimmunol. Photomed. 17, 203-212, 2001]* and as components of cosmetic preparations such as crèmes and lotions *[Weiner et al., J. Drug Target. 2, 405-410,,1994]*. Usually, liposomes have been used in their aqueous dispersed form, or have been incorporated in a gel-forming matrix including pharmaceutically used crème bases or hydrogels.

However, several types of phospholipid gels and their respective manufacturing processes have also been reported. Ghyczy and co-workers *[Ghyczy et al., EP 0514435 B1]* describe an alcoholic phospholipid gel with a phospholipid content of 15-30% and 14-20% alcohol. Three-dimensional liposome networks of highly concentrated (60%) semi-solid phospholipid dispersions have been designed and characterized by Brandl and co-workers *[Brandl et al., Adv. Drug Deliv. Rev. 24, 161-164, 1997; Brandl et al., Chem. Physs. Lipids 87, 65-72, 1997; Brandl et al. US 6,399,094]*. Vesicular phospholipid gels consisting of 40% phosphatidylcholine and cholesterol have been employed as carriers of anticancer agents for localized treatment of cancer *[Moog et al., J. Liposome Res. 8, 87-88, 1998; Güthlein et al., J. Liposome Res. 10, 251-252, 2000; Unger et al., WO 99/49716]*. Ibscher *[Dissertation, University of Freiburg, Germany, 2000; Ibscher & Fridrich, WO 01/13887 A2]* designed a phospholipid gel consisting of phospholipids, alcohols and sugar alcohols or carbohydrates as a topical carrier for antiviral skin treatment. Vesicular systems consisting of low phospholipid content (2%) and high alcohol content (30%), so-called ethosomes for topical use and transport of active agents into skin have also been reported *[Touitou et al., J. Control. Release 3, 403-418, 2000; Dayan & Touitou, Biomaterials 21, 1879-1885, 2000; Touitou, WO 95/35095]*.

In contrast to the above systems, it was surprisingly found that neutral and negatively charged phospholipids when combined at low concentration in water form spontaneously gels that are strong enough to be handled, e.g. filled into containers or syringes, and applied to human skin or body compartments.

Subject matter of present invention is a phospholipid gel consisting of a neutral and a negatively charged phospholipid and water.

The phospholipids used in the gels of present invention may be selected from natural, semi-synthetic or synthetic phospholipids.

Preferred embodiments of present invention are described in subclaims 2 to 11.

Soy phosphatidylcholine at concentrations of 10-20% and phosphatidylglycerol at concentrations of 2.5-10% when combined with water forms spontaneously a gel. This can also be accomplished with synthetic phosphatidylcholine/phosphatidylglycerol combinations such as dipalmitoylphosphatidylcholine and dipalmitoylphosphatidylglycerol or dimyristoylphosphatidylglycerol. The gel forms spontaneously from a thin lipid film when dispersed under mild agitation in water.

Dispersion under high shear or high pressure (homogenization) is not required. No organic solvents, detergents, or bridge-forming divalent ions need to be present. Active agents may be incorporated in the gel, specifically ubiquinone-type substances such as coenzyme Q10 can be present without interrupting the formation and retention of the gel structure.

Examples

Example 1

1A: 180 mg soy phosphatidylcholine and 20 mg egg phosphatidylglycerol are deposited as a thin film on a glass wall. 1 ml of distilled water is added and the container agitated on a shaker at low speed until a gel has formed. The gel is transferred to a syringe and stored at 4°C..

1B: The same procedure is employed to form a gel containing 190 mg phosphatidylcholine and 10 mg phosphatidylglycerol.

1C: The same procedure is employed to form a gel containing 195 mg phosphatidylcholine and 5 mg phosphatidylglycerol.

1D: The same procedure is employed to form a gel containing 90 mg phosphatidylcholine and 10 mg phosphatidylglycerol.

1E: The same procedure is employed to form a gel containing 360 mg phosphatidylcholine and 40 mg phosphatidylglycerol.

Example 2

2A: 150 mg Dipalmitoylphosphatidylcholine and 15 mg dimyristoylphosphatidylglycerol are deposited as a thin film on a glass wall. 1 ml of distilled water is added and the container agitated on a shaker at low speed until a gel has formed. The gel is transferred to a syringe and stored at 4°C..

2B: The same procedure is employed to form a gel containing 100 mg dipalmitoylphosphatidylcholine and 10 mg dimyristoylphosphatidylglycerol.

2C: The same procedure is employed to form a gel containing 60 mg dipalmitoylphosphatidylcholine and 6 mg dimyristoylphosphatidylglycerol

Example 3

180 mg Dipalmitoylphosphatidylcholine and 20 mg dimyristoylphosphatidylglycerol are combined with 30 mg conenzyme Q10 in chloroform. The organic solvent is evaporated under vacuum and the remaining phospholipid-Q10 mixture deposited as a thin film on a glass wall. 1 ml of distilled water is added and the container agitated on a shaker at low speed until a gel has formed. The gel is transferred to a plastic container and stored at 4°C..

Claims

1. A phospholipid gel consisting of a neutral and a negatively charged phospholipid and water.

2. A phospholipid gel according to claim 1, where the two phospholipid components are either of natural, semi-synthetic or synthetic origin.

3. A phospholipid gel according to claim 1 or 2, where the two phospholipid components are selected from di(C_8-C_{22}-acyl)phosphatidylcholine, preferably dipalmitoylphosphatidylcholine and di(C_8-C_{22}-acyl)phosphatidylglycerol, preferably dimyristoylphosphatidylglycerol.

4. A phospholipid gel according to any of claims 1 to 3, where the total phospholipid concentration is in the range of 6-40 weight %.

5. A phospholipid gel according to claims 3 to 4, where the ratio of phosphatidylcholine to phosphatidylglycerol is in the range of 10:1 to 10:0.25.

6. A phospholipid gel according to any of claims 1 to 5, containing a pharmacologically active agent.

7. A phospholipid gel of claim 6, where the active agent is a steroid, a non-steroidal anti-inflammatory agent, an antibiotic or an antioxidant.

8. A phospholipid gel of claim 7, where the steroid is selected from the group consisting of cholesterol, hydrocortisone, or dexamethasone, the non-steroidal anti-inflammatory agent is selected from the group consisting of ibuprofen, diclofenac, flurbiprofen, or nabumetone, the antibiotic is selected from the group consisting of tetracycline or its derivatives, an aminoglycoside e.g. gentamicin, neomycine, a macrolid-anlbiotic e.g. erythromycin, a nitroimidazol derivative e.g. metronidazol, or fucidinic acid, an antibiotic peptide, or an antibiotic oligondeoxynucleotide, the antioxidant is vitamin E or conezyme Q10.

9. A phospholipid gel according to any of claims 1 to 8, derived at by any useful preparation technique including shaking, vortexing, impeller mixing, extrusion, and homogenization.

10. Use of the phospholipid gel according to any of claims 1 to 9 as a moisturizing or mollifying agent on normal or diseased skin or mucosal membranes.

11. Use of the phospholipid gel according to any of claims 1 to 9 as a carrier for drugs or cosmetic substances to be applied to skin, mucosal membranes, body cavities of natural and surgical origin, and body compartments accessible by local or parenteral application.

Summary

In contrast to the above systems, it was surprisingly found that neutral and negatively charged phospholipids when combined at low concentration in water form spontaneously gels that are strong enough to be handled, e.g. filled into containers or syringes, and applied to human skin or body compartments.